## REMARKS

Status of the claims

Claims 21-36 are pending and under consideration in this application, claims 1-20 having been cancelled without prejudice to their being presented in a separate application. All the pending claims stand rejected. After entry of the amendments made herein, claims 21 and 37-43 will be pending in this application, claims 22-36 having been cancelled without prejudice to their being presented in a separate application, and new claims 37-43 having been added herein. New claims 37 and 39 are supported by the specification, e.g., in Examples 3, 4 and 5 (including Figures 4 and 5 and Tables 1 and 2) and page 11, lines 15-20. New claim 38 is supported by the specification, e.g., by the combined text on: page 2, line 25, to page 3, line 8; page 8, lines 12-22; and page 11, lines 15-20. New claim 40 is supported by the specification, e.g., in all the sections referred to above. New claim 41 is supported by claim 3 as originally filed and by the specification, e.g., at page 10, line 14, to page 11, line 6. New claims 42-43 are supported by the specification. e.g., at page 11, lines 15-25. No new matter is added by any of the new claims or by any of the amendments made herein.

Informality in the specification

Applicants have amended the specification as requested on page 2, lines 5-7, of the Office Action.

Informality in the claims

Applicants have amended claim 21 as requested on page 2, lines 9-11, of the Office Action.

35 U.S.C. § 112, first paragraph, rejection

Claims 23, 25, 27, 29, and 33 stand rejected as allegedly containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the

relevant art that that the inventors, at the time the application was filed, had possession of the claimed invention.

Applicants submit that the rejection is moot in light of the cancellation of all the above-listed claims.

35 U.S.C. § 112, second paragraph, rejections

Claims 21-36 stand rejected as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter that applicants regard as the invention.

Applicants have cancelled claims 22-36 and thus rejections of them are moot.

In regard to the comments on page 3, lines 17-20, of the Office Action, Applicants have amended claim 21 as suggested by the Examiner.

In regard to the comments on page 3, line 21, to page 4, line 3, Applicants have amended claim 21 by deleting the clause starting "comparing the determined concentrations with a reference value. . ." and have replaced it with a "wherein" clause containing an abbreviated version of it combined with language similar to that suggested by the Examiner for a correlation step. This amendment is supported by the specification, e.g., at page 11, lines 15-20. Applicants respectfully submit that such "wherein" clauses are frequently used in claims specifying diagnostic methods and the amendment provides the clarity required by the Examiner.

Other formality amendments to claim 21 serve to further enhance its clarity.

In view of the above amendments, Applicants respectfully submit that claim 21 is clear and request that the rejection under 35 U.S.C. § 112, second paragraph, be withdrawn.

35 U.S.C. § 103(a) rejections

Claims 21, 22, 24, 26, 28, and 36 stand rejected as allegedly being unpatentable over Hoffman et al. Applicants respectfully traverse this rejection.

Claims 22, 24, 26, 28, and 36 have been cancelled and thus rejections of them are moot.

From the comments on page 7, lines 19, to page 8, line 15, of the Office Action, Applicants understand the Examiner's position (with respect to claim 21) to be that, while

Hoffman et al. does not disclose increased levels of human lipocalin-type prostaglandin D synthase (L-PGDS; β-trace protein) in the urine of patients' with renal failure, because the reference teaches (a) elevated levels of the L-PGDS in the serum of patients with renal disease and (b) the presence of L-PGDS in urine, it would be obvious to one of ordinary skill in the art that there would be elevated levels of L-PGDS in the urine of patients with renal disease. Applicants strongly disagree with this position.

Applicants submit that elevation of the level a biological molecule (e.g., L-PGDS) in a first body fluid (e.g., urine) in a pathological condition of interest (e.g., renal failure) cannot be predicted by the mere fact of an elevated level of the same biological molecule in a second body fluid (e.g., blood). Indeed, one of skill in the art would readily envisage circumstances under which the relative levels of a biological molecule in two bodily fluids either would not be correlated or would be negatively correlated. Consistent with this view, in an article published after the priority date of the instant application [Hirawa et al., Nephron 87:321-327, 2001; copy enclosed as Exhibit A], it was reported that there is no relationship between plasma L-PGDS concentration and the level of urinary L-PGDS (see, for example, the Abstract).

Because it would not be obvious from Hoffman et al. that there are elevated levels of L-PGDS in the urine of early stage, or indeed any stage, renal disease, claim 21 is not obvious over Hoffman et al.

New claims 37-40 specify methods of diagnosing early renal diseases at defined stages of early renal disease, i.e., prior to enhanced serum creatinine levels, proteinuria, enhanced urinary albumin levels, or all three of these indications. These claims are amply supported by the specification, e.g., in the sections cited for support in the Status of the Claims section above. In addition, a scientific article published after the priority date of the instant application (Priem et al. Clinical Chemistry 45(4):567-568, 1999; copy enclosed as Exhibit B) provides confirmatory evidence of the ability to detect early renal disease by measuring the level of L-PGDS (designated β-trace protein (BTP) in the article) in sera from subjects suspected of having an early stage of the disease, i.e., prior to significantly enhanced levels of serum creatinine (see, e.g., page 567, column 2, paragraph 3, to page 568, column 1, paragraph 1).

In light of the only data shown in Hoffman et al. on renal disease patients being from patients with chronic/terminal renal failure, Applicants submit that, with respect to new claims 37-40, the supposition in Hoffman et al. ("we suppose that especially in early diagnosis of renal diseases . . . [β trace protein] may become a much more reliable and sensitive parameter") is pure conjecture and provides no more than "an invitation to try" without the least assurance of success. Moreover, Hoffman et al. uses a general term ("early diagnosis of renal diseases") and gives no hint as to exactly what is meant by "early diagnosis of renal diseases", how early "early diagnosis of renal diseases" is, or at what early stage of renal disease measurement of L-PGDS serum levels will be useful. On the other hand, new claims 37-40 clearly define relevant early stages of renal diseases in terms of independent clinical parameters at which blood levels of L-PGDS can be measured. Thus, in the methods specified by these claims, measurements of L-PGDS concentrations are made prior to: enhanced serum creatinine levels; proteinuria; enhanced urinary albumin levels; or all three of these indications. There is no suggestion or motivation in Hoffman et al. to determine L-PGDS levels at these particular early stages of renal disease.

With reference to the Examiner's position that in disclosing "the use of healthy control patients" Hoffman et al. teaches the testing of subjects prior to diagnosis of early nephropathy (Office Action, page 8, lines 16-20), Applicants point out that in the instant claims the relevant subjects are test subjects, which are by definition not "healthy control patients". Applicants respectfully submit that one of ordinary skill in the art would not be motivated by the disclosure in Hoffman et al. of the "use of healthy control patients" to apply the tests for the diagnosis of early renal disease to test subjects as specified by claims 37-40.

In light of the above considerations, Applicants respectfully submit that the invention specified by the above-listed claims is not obvious in view of Hoffman et al. and thus request that the rejection under 35 U.S.C. §103(a) be withdrawn.

## CONCLUSION

In summary, for the reasons set forth above, Applicants maintain that the pending claims patentably define the invention. Applicants request that the Examiner reconsider the rejections as set forth in the Office Action, and permit the pending claims to pass to allowance.

If the Examiner would like to discuss any of the issues raised in the Office Action, Applicants' undersigned representative can be reached at the telephone number listed below.

Enclosed is a request for an automatic extension of time and a check in payment of the extension in time. Please apply any other charges or credits to Deposit Account No. 06-1050, referencing Attorney Docket No. 11283-009001.

Respectfully submitted,

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